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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,251	02/20/2004	Laura C. Blumberg	PC25698A	1409

28523 7590 01/24/2007

PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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EXAMINER	
MOORE, SUSANNA	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,251	BLUMBERG ET AL.	
	Examiner	Art Unit	
	Susanna Moore	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5,6(part),7-12 and 13(part)* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6(part),13(part),14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18,9/22,10/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

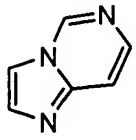
DETAILED ACTION

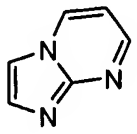
Response to Amendment

Applicant's election of Group (I), claims 1-4, 6(part), 13(part), 14 and 15 in the reply filed on 11/27/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The status of the claims is as follows: claims 1-4, 6(part), 13(part), 14 and 15 are pending. Claims 5 and 8-12 are withdrawn.

There are some species that were removed by amendment which belong in Group (I) and others which were not removed that do not belong in Group (I). To clarify the elected invention, Applicant elected Group (I) drawn to imidazopyrimidines. The following structures illustrate the 2 cores elected.





Thus, claim 6 should be amended to exclude structures that are not part of the elected invention. Claim 7 is withdrawn and should be labeled as such. Claim 13 should have all nonelected cores (e.g. imidazopyridines) removed and elected species (i.e. imidazopyrimidines) reinstated. The definition of R4 and R6 taken together in claim 1 should be limited to the elected "pyrimidine," i.e. "R4 and R6 taken together with the atoms to which they are attached form a

pyrimidine." Also, claim 15 is mislabeled as withdrawn; it is an original claim. The current set of claims has elected subject matter removed but the Examiner assumes this is in error.

This application contains claims drawn to an invention nonelected in Paper No. 11/27/06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-4, 6(part), 13(part)-15 are rejected as drawn to an improper Markush group, as these claims contain both elected and non-elected subject matter, which are parts of different inventions. The choices are not art-recognized equivalents for reasons set forth in the requirement for restriction. Deletion of non-elected subject matter as indicated above will overcome the rejection.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Imidazopyrimidines as Transforming Growth Factor (TGF) Inhibitors.

Claim Objections

Claim 1 is objected to because of the following informalities: the phrase "at least one" is repeated in 6th line from the bottom of the page. Appropriate correction is required.

Claims 1, 6, 7 and 13 are objected to because of the following informalities: the claims contain nonelected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity

of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. The instant claims encompass millions of compounds with a imidazo[1,2-a]pyrimidine scaffold with a variety of substituents at two different positions.

(b) Scope of the diseases covered. The instant claims are drawn to a method of treating cancer, glomerulonephritis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis, intimal hyperplasia, restenosis, scleroderma and dermal scarring. The scope is broad, and as a result, several of the umbrella terms are further defined.

Cancers are classified by the type of cell that resembles the tumor and, therefore, the tissue presumed to be the origin of the tumor. The following general categories are usually accepted:

- Carcinoma: malignant tumors derived from epithelial cells.
- Lymphoma and Leukemia: malignant tumors derived from blood and bone marrow cells
- Sarcoma: malignant tumors derived from connective tissue, or mesenchymal cells.
- Mesothelioma: tumors derived from the mesothelial cells lining the peritoneum and the pleura.
- Glioma: tumors derived from glia, the most common type of brain cell.
- germ cell tumours: tumors derived from germ cells, normally found in the testicle and ovary.
- Choriocarcinoma: malignant tumors derived from the placenta.

Cancers include the following, but are not limited to: (topography) eye, endometrium, bladder, breast, colon, penis, kidney, liver, lung, brain, small cell lung cancer, esophogus, gall bladder, ovary, pancreas, stomach, cervix, colon/rectum, mouth, larynx, head/neck, thyroid, prostate, testicle, skin, squamous cell carcinoma, anus and leukemia; (cell type/morphology) acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, Burgett's lymphoma, acute myelogenous leukemia, chronic myelogenous leukemia, myelodyplastic syndrome, promyelocytic leukemia, fibrosarcoma, rhabdomyosarcoma, astrocytoma, neuroblastoma, glioma, schwannomas, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer, Kaposi's sarcoma, angiosarcoma, dermatofibrosarcoma, desmoid tumor, desmoplastic small round cell tumor, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, hemangiopericytoma, hemangiosarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, synovial sarcoma, Askin's Tumor, Ewing's sarcoma and alignant hemangioendothelioma.

Stenosis is the narrowing of a blood vessel or other tubular organ. Restenosis just means the recurrence of this condition. There are different causes, such as atherosclerosis, birth defects, ischaemia, infection, neoplasm and inflammation. Examples of various stenotic lesions are, but not limited to: intermittent claudication (peripheral artery stenosis), angina (coronary artery stenosis), obstructive jaundice (biliary tract stenosis), carotid artery stenosis (strokes and transient ischaemic episodes), pyloric stenosis (gastric outflow obstruction), renal artery stenosis,

hydrocephalus, stenosing tenosynovitis, spinal stenosis, subglottic stenosis (SGS) and bowel obstruction.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information, found on page 51 of the Specification gives 0.1-200 mg, one to four times per day, which is broad and generic, the same for the many disorders covered by the Specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for any and all the diseases listed under the Scope above.

(D) State of the Prior Art: These compounds are imidazo[1,2-a]pyrimidines with a particular substitution at two different positions. So far as the examiner is aware, no substituted imidazopyrimidines with this particular substitution have been used for treating all the diseases and conditions listed under the Scope above.

(E) Working Examples: The invention is drawn to a method of treating cancer, glomerulonephritis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis, intimal

hyperplasia, restenosis, scleroderma and dermal scarring. On pages 54-55 of the Specification there are two in vitro assays presented, a TGFbetaII activation assay and an ALK5 activation assay. No standard assays were conducted for anti-cancer activity in the form of an in vitro assay or mammal models.

(F) Skill of those in the art: These diseases and disorders cannot be treated generally by any one drug. These are all different diseases and disorders, which occur at different locations and by different modes of action in the body.

The state of the art prior to Applicants effective filing date is presented by Strutz (Expert Opin. Investig. Drugs, 2001, 10(11), pages 1989-2001). On page 1994, section 5.2, the bottom the left hand column, pertains to inhibiting TGFbeta1. Strutz presents support for the treatment of glomerulonephritis, diabetic nephropathy, hepatic fibrosis and pulmonary fibrosis. See the right hand column, the first and second paragraph, on page 1994. Thus, Applicants are enabled for these diseases.

Renal failure is the condition in which the kidneys fail to function properly. It can be classified into two categories, acute and chronic. End stage renal failure itself, a form of chronic renal failure, is only treatable by dialysis and transplantation, not pharmaceuticals.

The prior art knows that there never has been a compound capable of treating cancer generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally."
(<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7
<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm>> ENABLEMENT DECISION

TREE, Example F, situation 1) There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology.

(G) The quantity of experimentation needed: Owing especially to factors A, C, E and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claims 1-4, 6, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to solvates. But the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton*

International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SM

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